PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:	EXAMINER: **Thomas Sweeney Heard**
Michael David Bentley, et al.	ART UNIT: **1654**
APPLICATION NO.: **10/647,561**	CONF. NO: **3230**
FILED: **August 25, 2003**	
FOR: **POLYMER STABILIZED NEUROPEPTIDES**	

APPELLANT'S BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Appeal Brief - Patents

Sir:

This is an appeal to the Board of Patent Appeals and Interferences from the Notice of Panel Decision from Pre-Appeal Brief Review mailed October 9, 2008, in the above-identified application in which pending claims 1-3, 6-16, 18, 19, 23, 24, 26, and 27 stand in final rejection.

The present paper is Appellant's Appeal Brief submitted in compliance with 37 C.F.R. § 41.37.

REAL PARTY IN INTEREST

The real party in interest is Nektar Therapeutics AL, Corporation, the assignee of record of all right, title and interest in the present application.

RELATED APPEALS AND INTERFERENCES

No other prior or pending appeals, interferences or judicial proceedings are known to the Appellant, the Appellant's legal representative, or Assignee, which may be related to, directly affect, or be directly affected by or have a bearing on, the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims 1-3, 6-16, 18, 19, 23, 24, 26, and 27 are pending and stand in final rejection. It is these claims that are the subject of this appeal. Claims 1-3, 6-19, 23, 26, and 27 are presented in Appendix A.

Claims 4, 5, 17, 20-22, and 25 are canceled without prejudice.

Claim 24 is currently withdrawn as being directed to a non-elected specie.

STATUS OF AMENDMENTS

A Pre-Appeal Brief Request for Review was filed on August 28, 2008, subsequent to the mailing date of the final Office action. A Notice of Panel Decision from Pre-Appeal Brief Review was mailed on October 9, 2008; the decision stated that there is at least one actual issue for appeal.

SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter defined by the claims is directed to water-soluble, polymer-peptide conjugates of neuropharmaceutical peptide agents. The peptide portion of the conjugate is either the neuropharmaceutical peptide agent biphalin, or the neuropharmaceutical peptide agent [D-Pen^2, D-Pen^5] enkephalin ("DPDPE"). [*See* claim 1, appendix A.] The neuropharmaceutical peptide agent is linked to one or more water-soluble polymer chains, such as poly(ethylene glycol), forming the polymer-peptide conjugate, in a process known as "PEGylation" when the polymer is a poly(ethylene glycol). [Specification at page 3, paragraph 26.] The polymer-peptide conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood-brain barrier ("BBB"). [Appellant's Specification at page 2, paragraph 12.] Thus, the polymer-peptide conjugate is able to affect a therapeutic result in the brain. [Claim 2, appendix A.]

Non-conjugated peptides fail to effectively cross the BBB. [Appellant's Specification at page 1, paragraph 8]. Such failure to cross the BBB severely limits the therapeutic effectiveness (or "efficacious effect") of such neuropharmaceutical peptide agents. However, Appellant has shown that a polymer-biphalin conjugate was able to pass through the BBB following administration, and has therapeutic effect (Figs. 1-6). [Appellant's Specification (Example 7) at page 8, paragraphs 94-115.] Additionally, Appellant has shown that the concentration of the polymer-DPDPE conjugate was significantly increased in the brain (Example 5) following its administration, rather than getting trapped outside of the brain in its un-conjugated form. [Appellant's Specification at page 7, paragraph 77.]

The polymer conjugates of neuroactive peptide agents of the present claims are able to pass through the BBB, and overcome the problems associated with prior methods of brain delivery (*e.g.*, failure to effectively cross the BBB). [Appellant's Specification at page 1, paragraph 8.]

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue for review on appeal is:

1. Whether claims 1-3, 6-19, 23, 26, and 27 are obvious under 35 U.S.C. § 103(a) over the combination of Delgado *et al.* (*Critical Reviews in Therapeutic Drug Carrier Systems*, 1992, vol. 9(3,4), 249-304, hereafter "Delgado"), Wu and Pardridge (*Proceedings of the National Academy of Sciences*, 1999, vol. 96, 254-259, hereafter "Wu"), and Sakane and Pardridge (*Pharmaceutical Research*, 1997, vol. 4(8), 1085-1091, hereafter "Sakane").[1]

Reconsideration of this rejection is respectfully requested. The issue to be addressed is whether a polymer conjugate of a neuropharmaceutical peptide that is biphalin or DPDPE, where the peptide conjugate ***must*** cross the BBB, is rendered obvious by combined references that in no uncertain terms ***teach away*** from the subject claim (discussed below). Appellant respectfully submits that the Examiner has failed to meet the requirements for establishing a *prima facie* case of obviousness.

[1] In the current Final Office Action, mailed May 28, 2008, the Examiner states that the prior rejection of claims 1-3, 5-19, 21, 23, and 27 under 35 U.S.C. § 103(a) as unpatentable over Delgado and Wu has been overcome in light of Appellant's amendment to the claims. (The claims were amended to recite a conjugate that "consists of" rather than "comprises" certain features). In view of the foregoing, the Examiner must therefore be relying on Sakane to make up the deficiencies of Delgado and Wu in the current and only remaining rejection.

ARGUMENT

I. Rejection under 35 U.S.C. §103(a)

The pending claims stand rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Delgado, Wu, and Sakane. [Final Office Action mailed May 28, 2008, at pages 3-4.]

The Examiner's grounds for this rejection, as well as Appellant's rebuttal thereto, follow.

A. The Claimed Invention

The claims under consideration are directed only to polymer conjugates of the neuropharmaceutical peptide agents biphalin or DPDPE. The polymer-peptide conjugates, as embodied in the sole independent claim (claim 1), consist of (i) a peptide that is either biphalin or DPDPE; (ii) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons, and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol; which (iii) when administered into the blood circulation of a mammal, is capable of ***transport across the BBB***. [Claim 1, appendix A (emphasis added.] Thus, the polymer conjugate is required to cross the BBB.

Dependent claim 2 recites the analgesic effect that BBB passage of the conjugated neuroactive peptide (biphalin or DPDPE) must have in the brain. [Claim 2, appendix A.]

Dependent claim 16 recites a pharmaceutical composition comprising the polymer-peptide neuropharmaceutical agent conjugate according to claim 1. [Claim 16, appendix A.]

The remaining dependent claims recite features of a given polymer, or the particular position where the polymer is linked to the peptide (biphalin or DPDPE), and the like.

The prior art relied upon by the Examiner at best teaches that the PEGylation of neuroactive ***proteins*** (*i.e.*, not peptides) improves the pharmacokinetic ("PK") properties of the PEGylated protein. PK profiles include properties such as the amount of time the modified protein exists in the blood, or how fast the kidneys excrete the modified protein. [*See* Final Office Action mailed May 28, 2008, at page 4 *citing* Delgado.] While the Appellant is in agreement with the Examiner regarding the beneficial nature of such improved PK properties, it is respectfully submitted that such improved PK properties are not relevant to the instant claims. Highly relevant however is the inescapable conclusion that the prior art relied upon by the Examiner teaches that PEGylation of neuroactive ***proteins*** actually ***inhibits*** passage of the neuroactive protein through the BBB (measured by the apparent brain volume of distribution). [*See e.g.* Sakane, Figure 4, page 1089–1090, and the following arguments.]

In addition to the ***teaching away*** from PEGylation to achieve transport into the BBB, the prior art relied upon by the Examiner further teaches that a receptor-specific portion of the conjugate protein was required to effectuate transport of the agent through the BBB. This "receptor-specific" portion was either (i) a "carrier protein" (which was taken up as a ligand by a specific receptor), or (ii) a monoclonal antibody specific to a particular receptor. [Sakane, page 1, paragraphs 7-9.] The claims of the present invention require neither a carrier protein nor monoclonal antibodies. In view of the cited prior art, the current invention is ***unexpected*** and ***surprising***.

B. The Cited Art: The Delgado, Wu, and Sakane Art

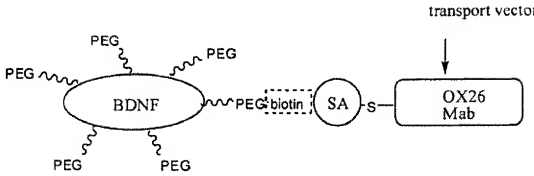
1. The Delgado Art

Delgado is a 1992 review article describing several PEGylated proteins, their pharmacological and chemical properties (antigenicity, renal clearance, bioactivity, etc.), methods of synthesis and analyses, and the like. Nowhere does Delgado suggest a biphalin or DPDPE peptide-polymer conjugate, let alone that such a conjugate is capable

of administration to the bloodstream and transport across the BBB, resulting in an analgesic effect. [*See generally* Delgado; *c.f.* Claims 1 and 2, appendix A].

2. The Wu Art

Wu describes a modification of the brain-derived neurotrophic factor ("BDNF") protein in order to provide a protein conjugate capable of transport across the BBB upon peripheral administration.



The structure of the Wu protein conjugate is provided pictorially above. As can be seen, the Wu conjugate employs the combined use of PEGylation technology (*e.g.*, the PEG chains surrounding the BDNF protein), antibody targeting (*e.g.*, the OX26 monoclonal antibody ("MAb") directed against the transferrin receptor located on the surface of endothelial cells making up the BBB), and avidin-biotin technology to link the PEGylated protein to the MAb ("biotin-SA" above). [Wu, page 254, column 2.]

Wu further describes the function of each component of the BDNF protein conjugate. Wu describes the PEG chains as preventing rapid uptake of the protein by peripheral tissues (a PK property), while the OX26 MAb functions as the transport vector that provides transport of the conjugate through the BBB, owing to high concentrations of the rat transferrin receptor on the brain capillary endothelium. Conjugation of the PEG segment to the OX26 MAb is accomplished via a biotin streptavidin complex. As Wu

clearly describes, transport of the above three-component conjugate is facilitated by the OX26 MAb transport vector - ***not*** by the PEG.

Nowhere does Wu describe or even remotely suggest preparing a BDNF conjugate protein wherein the BDNF protein is conjugated to PEG for transport across the BBB. Indeed, quite the opposite is true. Wu states that BDNF ***must be*** (i) conjugated to a BBB drug delivery system (*i.e.*, OX26 MAb), ***and*** (ii) PEGylated to improve PK properties. [Wu at page 257.] Thus, to modify Wu in order to arrive at a conjugate of the present invention would be to ***go against the very teachings*** of Wu by eliminating a feature described therein as ***essential*** to the invention (*i.e.*, the transport vector, among the four "important" or "critical" factors). [*Id.*]

3. The Sakane Art

Sakane is newly cited art by the Examiner. Sakane describes methods for carboxyl-directed PEGylation of the BDNF protein to improve its PK profile without adversely effecting the protein's biological activity or efficacy (as reportedly occurs with modification of surface lysine residues of nerve growth factor-like neurotrophins). In fact, Sakane similarly states that attachment of PEGylated BDNF protein to a MAb/avidin "delivery system" facilitates delivery through the BBB. [Sakane at page 1090.]

As an initial matter, and as noted above, the Examiner states that the prior rejection of claims 1-3, 5-19, 21, 23, and 27 under 35 U.S.C. § 103(a) as unpatentable over Delgado and Wu was overcome in light of Appellant's amendment to the claims. [Final Office Action mailed May 28, 2008, at page 2.] Thus, the Examiner must be relying on Sakane to make up the deficiencies of Delgado and Wu in the current and only remaining rejection. The Sakane and Wu references originate from the same research group, and are at best cumulative. Thus, withdrawal of the rejections based on Wu cannot be re-asserted based on the cumulative Sakane reference alone. On this basis it appears the Examiner has failed to meet the required *prima facie* case by relying on a cumulative prior art reference to reject the claims when amendments to those

claims successfully traversed Wu. The Examiner states that Sakane teaches "optimized pharmacokinetics" of PEGylated proteins. [Final Office Action mailed May 28, 2008, at page 5.] Thus, the Examiner is focused on PK profiles of PEGylated proteins.

Although Appellant agrees with the Examiner that Sakane does indeed describe that the PK profile of the BDNF protein is improved by carboxyl-directed conjugation with PEG-2000 and PEG-5000, this point is irrelevant to the instant appeal. While improved PK profiles or "optimized properties" as the Examiner describes them, are certainly desirable, PK profiles ***are not*** what are claimed by the Appellant. Rather, the Appellant claims that a PEGylated neuropeptide (biphalin or DPDPE, ***not a protein***) that crosses the BBB following administration into the blood.

Furthermore, and far more relevant to the instant analysis, is that Sakane ***teaches away*** from PEGylation as a means to facilitate BBB passage because the brain volume of distribution of the PEGylated BDNF protein is ***inhibited*** following PEGylation with either PEG-2000 or PEG-5000. [*See e.g.* Sakane, Exhibit 4, at page 1089.] This absolutely critical scientific data was apparently overlooked by the Examiner, and cripples his assertion of a "reasonable expectation of success in producing the claimed invention" [Final Office Action mailed May 28, 2008, at page 6.] There is simply no reasonable basis supporting the Examiner's assertion that one skilled in the art could possibly conclude that PEGylation alone of a ***neuropeptide*** to effectuate ***BBB transport*** into the brain was obvious in light of Sakane and Wu – art in fact teaching that PEGylation of a ***protein inhibited BBB transport***.

As mentioned above, Sakane also suggests that PEGylated BDNF protein as prepared must be further modified by attachment to a MAb/avidin delivery system in order to effectuate delivery through the BBB [Sakane at page 1090.] In essence, to overcome the ***inhibitory*** effect of PEGylation, conjugation to a targeting system was required. Thus, Sakane, as does Wu, ***teaches away*** from the Appellant's claims by suggesting that if transport across the BBB is desired, one must further modify the PEGylated protein by attaching a biotin moiety, which must then must be further attached

to a MAb/avidin delivery system. Such an approach clearly falls outside of the Appellant's claims, and cannot be reasonably argued to constitute prior art that one skilled in the art would be motivated to combine or modify under 35 U.S.C. §103(a) in order to render the instant pending claims obvious.

C. Examiner's Position

It is the Examiner's assertion that the prior art renders obvious the instant claims because: (i) Delgado teaches beneficial uses of various PEGylated forms of proteins, (ii) that Wu teaches the PEGylation of the protein BDNF (erroneously called a "peptide") to improve PK profiles (what the Examiner calls "optimized properties"), and (iii) that Sakane teaches "optimized" PK profiles following PEGylation, in accord with Delgado and Wu. [*See* Final Office Action mailed May 28, 2008.]

It is thus clear that the Examiner relied upon on the purported improved PK profile of the PEGylated BDNF ***protein*** (which ***inhibits*** BBB transport) to reject the instant claims of a particular PEGylated ***peptide*** (which ***facilitates*** BBB transport). The Examiner's assertion is respectfully refuted.

D. Appellant's Rebuttal

The issue is whether one skilled in the art, having the three cited references in hand, would have arrived at the Appellant's claimed invention. The Appellant respectfully submits that the answer to this question is "no", for the reasons that follow.

As reiterated by the Supreme Court in *KSR*, the framework for making an objective determination of obviousness is stated in *Graham.* [*KSR International Co. v. Teleflex, Inc.*, 82 USPQ2d 1385, 1391 (2007) *citing Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), *see also* M.P.E.P. § 2141.] Such an objective determination must include consideration of the claimed invention ***as a whole***, and also a consideration of the prior art references as a whole (***including disclosures that teach away from the***

claims). [*Id.*] Appellant respectfully submits the Examiner failed to consider the invention as a whole, and overlooked disclosures that teach away from the instant claims.

1. The Examiner Failed to Establish a *Prima Facie* Case

The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the rationale for such a rejection. The Supreme Court has articulated, and this body has adopted, exemplary rationales supporting a conclusion of obviousness. [*See* M.P.E.P. §2141; *see also generally KSR* and the identified rationales supporting an obviousness rejection.] The Examiner has failed to clearly articulate a rationale supporting the obviousness rejection. The Examiner must consider whether one of ordinary skill in the art at the time of the invention would be prompted, with a reasonable expectation of success, to combine the alleged prior art elements. Or stated another way, "the operative question is thus 'whether the improvement is more than the predictable use of prior art elements....'" [*See* M.P.E.P. §2141, citing *KSR*.] Quite the opposite is true here: there was no expectation of success or predictable use.

a. *Failure to Appreciate the Lack of Predictable Results*

The prior art relied upon by the Examiner clearly indicates there was ***no*** expectation of success or predictable use of the prior art elements. The Examiner appears to base his rejection on PK profile improvements of PEGylated proteins in general cited in the prior art. Such an assertion, besides appearing to be a non sequitur, ignores the total ***unpredictability*** of the instant invention. [*see Federal Register,* vol. 72, No. 195 indicating that a combination of prior art elements should yield "predictable results"; *see also* M.P.E.P § 2141; *see also generally KSR*.] The Appellant submits that there is nothing in the prior art relied upon by the Examiner to lead one of skill in the art to combine or modify those elements in such a way as to predict the results of the claimed invention. Indeed, it is respectfully submitted that the Examiner has neglected to recognize the ***unpredictable nature of***, and the ***teaching away from***, the instant claims

in view of the prior art of record which teaches inhibition of transport across the BBB following PEGylation. It is submitted with the utmost respect that the Examiner has clearly failed to appreciate the unpredictable results of the instant claims which ***require*** transport of a ***peptide*** across the BBB following PEGylation. In view of the foregoing, a *prima facie* case of obviousness has not been made, and the rejection cannot be sustained.

b. *Failure to Consider the Claimed Invention as a Whole*

The claimed invention, when considered as a whole, is directed to polymer conjugates of biphalin or DPDPE that must cross the BBB following introduction into the blood. While improved PK profiles might be present and even desirable, the claims were not drafted to such "improved properties", but rather to PEGylated neuropeptides that must cross the BBB following administration into the blood of a mammal. The Examiner has failed to view the claims as a whole in this regard, and has instead focused on irrelevant PK properties not claimed in the instant application.

c. *Failure to Consider the References as a Whole*

Appellant submits that in characterizing the prior art references, the Examiner has failed to consider the teachings of these references as a whole, and had taken the teachings of these references out of context. Most notably, two of the three references (Wu and Sakane) clearly ***teach away*** from the claimed invention.

(i) Delgado is merely a review

Delgado is a review article describing various PEGylated ***proteins*** (not peptides) and their pharmacological properties, including methods of synthesis and analysis. Delgado has nothing to do with small peptides such as biphalin ((Try-D-Ala-Gly-Phe-NH)$_2$) or DPDPE (Tyr-D-Pen-Gly-Phe-D-Pen), and is completely silent regarding the

impact of PEGylation on the ability of any compound, let alone a small peptide such as biphalin or DPDPE, to cross the BBB. The Examiner agrees that Delgado does not teach the PEGylation of neuropeptides (BDNF and biphalin in particular). [Final Office Action mailed May 28, 2008, at page 5.]

(ii) Wu teaches away from the claimed invention

Wu describes the modification BDNF (a 27.0 kDa ***protein***) via PEGylation to improve its PK properties, not to enable transport across the BBB. Specifically, Wu states that conjugation of the PEGylated BDNF protein to an OX26 MAb (the transport vector) ***is required*** to facilitate transport of the BDNF protein across the BBB (*See* Abstract). Wu stresses that for a neurofactor like the BDNF protein to have therapeutic utility, it is required that the protein be modified to both improve its plasma PK properties (the PEGylation step) **and** to enable transport across of the BBB (the coupling of the BDNF to a transport vector such as OX26 MAb step). For example, Wu states "[t]he results of the present investigation indicate that if the neurotrophic factor undergoes a defined molecular reformulation, such as that depicted in Fig. 1, ***both*** to enable BBB transport and to optimize plasma pharmacokinetics, then these molecules may have therapeutic effects in the brain after peripheral administration." [Wu at page 258 (emphasis added).] When viewed as a whole, it is clear Wu teaches that the therapeutic neurofactor protein BDNF must be conjugated to a transport vector to facilitate crossing of the BBB into the brain.

Given the teachings of Wu, the subject matter of the Appellant's claims (which recite a conjugate ***consisting of*** a ***peptide*** that is either biphalin or DPDPE, covalently linked to one or more water-soluble polymer chains, which when administered into the blood circulation of a mammal, is capable of ***transport across the BBB***) is absolutely unpredictable. In no way can the modification of the teachings of Wu -- to omit a so described "critical" element responsible for the transport of the protein across the BBB

(*i.e.*, the transport vector portion) -- be considered a predictable modification of the art. Such an assertion cannot be deemed grounds for rejection under 35 U.S.C. §103.

(iii) Sakane teaches away from the claimed invention

In further support of the untenable position the Examiner has taken, the teachings of Sakane are entirely consistent with Wu in the ***teaching away*** from the instant claims. Sakane teaches that in order to impart the ability of the PEGylated BDNF protein to cross the BBB, the PEGylated BDNF must be further conjugated to a transport vector. [*See* Wu at page 1090, stating in part "[t]hese results suggest that neurotrophins may be converted into more effective neuropharmaceuticals through drug delivery strategies that place importance on the ***dual task*** of optimizing both plasma pharmacokinetics, (with the use of pegylation technology), and ***transcellular membrane transport,*** [sic] ***(with the use of vector-mediated drug delivery systems)***." (emphasis added).]

Indeed, when considering the reference as a whole, Sakane demonstrates that BBB passage of the BDNF protein is ***inhibited*** upon PEGylation, and that BDNF protein ***must be*** coupled to a delivery system that enables BBB transport. [*See* Sakane, at 1085, stating "However, BDNF does not cross the brain capillary endothelial wall, which makes up the blood-brain barrier (BBB) in vivo."] Thus, the art relied upon by the Examiner provides absolutely no reason for one of skill in the art to combine/modify the elements in the way that the claimed invention does in order to achieve a conjugate capable of transport across the BBB. Indeed, the art relied upon by the Examiner suggest the exact opposite.

Since Sakane (i) fails to provide even the slightest rationale for modifying the conjugates therein to arrive at conjugates of the type administered by the Appellants, and in fact; (ii) points to the undesirability of administering conjugates of the type administered by the Appellants; and further (iii) describes that such conjugates are

unsatisfactory due to their inability for effective transport across the BBB – the reference of Sakane, like that of Wu, must fail to render obvious the Appellant's claims.

d. *Peptides Are Not the Same as Proteins*:

As mentioned above, the art relied upon by the Examiner is directed to large proteins such as BDNF, rather than small neuropeptides (and much less the type of neuropeptides currently recited in the claims). When considered as a whole, it is submitted that Examiner has not given proper consideration to the surprising and unpredictable finding that the small neuropeptides biphalin and DPDPE, conjugated to large water-soluble polymers, retain their biological activity and are able to cross the BBB. For example, Appellant demonstrates that: (i) biphalin or DPDPE conjugated to PEG are able to cross the BBB barrier and produce an analgesic effect *in vivo* after intravenous injection in mice [paragraphs 94-97, and Figures 2-6]; (ii) PEG-DPDPE produces an analgesic effect [paragraph 94 and Figure 2], (iii) PEGylation of DPDPE significantly prolongs the duration of analgesic effect; and (iv) all PEGylated biphalin exhibited a potent analgesic response in mice, with a maximum response of 80-90% M.P.E. reached between 30-45 minutes [paragraph 95]. Contrasted to the findings reported by Wu and Sakane, it is clear that small peptides are very different to that of large proteins. It is respectfully submitted that the Examiner failed to appreciate this difference.

2. The Prior Art Relied Upon by the Examiner Cannot Support an Obviousness Rejection

For the foregoing reasons, it is submitted that compounds having the features recited in the instant claims (PEGylated biphalin or DPDPE) and having the ability to cross the BBB to produce an analgesic effect, are surprising and unexpected in view of the art of record.

Nowhere has the Examiner identified any reason that would have prompted a person of ordinary skill in the art to modify or combine the disparate and contradictory elements of the art relied upon by the Examiner to arrive at the Appellant's claimed invention – a factor acknowledged by the Court in *KSR* (ibid) as relevant in a finding of obviousness. Indeed, the Appellant fails to find in the references even the slightest rationale for omitting what are described as an essential or critical elements for effectuating BBB transport of neuroactive proteins with any hope for a degree of success. Indeed, the opposite is true: the prior are clearly teaches away form the claimed invention. In view of the foregoing, in no way can the Appellant's claimed peptide conjugates be considered to have been predictable to a person of ordinary skill in the art.

Appellant respectfully submits that there is clear deficiency in the *prima facie* case put forward by the Examiner. Appellant further respectfully submits that all of the pending claims are in condition for allowance and patentably define over the prior art. Withdrawal of the outstanding rejection under 35 U.S.C. §103(a), and a favorable decision on the allowability of the pending claims is requested.

Respectfully submitted,

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CLAIMS APPENDIX

1. A hydrophilic polymer-peptide conjugate consisting of a peptide that is either biphalin or [D-Pen^2, D-Pen^5) enkephalin (DPDPE) covalently linked to one or more water-soluble polymer chains having a molecular weight from about 2,000 to about 100,000 daltons and selected from either poly(ethylene glycol) or copolymers of ethylene glycol and propylene glycol, wherein said conjugate, when administered into the blood circulation of a mammal, is capable of transport across the blood brain barrier.

2. The conjugate of Claim 1, which, when administered to the blood circulation of a mammal, has an extended duration of analgesic effect when compared to the corresponding unconjugated peptide.

3. The conjugate of Claim 1, wherein said one or more water soluble polymer chains is absent one or more lipophilic moieties.

4 - 5. (Canceled).

6. The conjugate of Claim 1, wherein said peptide is covalently linked to at least one terminus of said one or more polymer chains.

7. The conjugate of Claim 1, wherein said peptide is covalently linked at an N-terminus to said one or more polymer chains.

8. The conjugate of Claim 1, wherein said water-soluble[[,]] polymer chain is a copolymer of polyethylene glycol and polypropylene glycol.

9. The conjugate of Claim 1, wherein said water-soluble polymer chain is polyethylene glycol.

10. The conjugate of Claim 9, wherein said polyethylene glycol is selected from the group consisting of monomethoxypolyethylene glycol, branched polyethylene glycol, polyethylene glycol with degradable linkages in the backbone, homobifunctional polyethylene glycol, heterobifunctional polyethylene glycol, multi-arm polyethylene glycol, pendant polyethylene glycol, and forked polyethylene glycol.

11. The conjugate of Claim 1, wherein said peptide is conjugated to a single polyethylene glycol chain.

12. The conjugate of Claim 1, comprising biphalin covalently attached to two polyethylene glycol chains.

13. The conjugate of Claim 1 wherein said polymer chain is polyethylene glycol having a nominal average molecular weight of about 2,000 daltons to about 40,000 daltons.

14. The conjugate of Claim 13 wherein said polyethylene glycol has a nominal average molecular weight selected from the group consisting of 2000 daltons, 5000 daltons, 8,000 daltons, 10,000 daltons, 12,000 daltons and 20,000 daltons.

15. The conjugate of Claim 13 wherein said polyethylene glycol has a nominal average molecular weight of 2,000 daltons.

16. A pharmaceutical composition comprising a conjugate according to Claim 1 and a pharmaceutically acceptable carrier.

17. (Canceled).

18. The conjugate of Claim 9, wherein said polymer chain is linear.

19. The conjugate of Claim 1, wherein said peptide is covalently linked to said one or more water soluble polymer chains at a tyrosine resude of said peptide.

20 - 22. (Canceled).

23. The conjugate of Claim 1 wherein said peptide is biphalin.

24. The conjugate of Claim 1 wherein said peptide is DPDPE.

25. (Canceled).

26. The conjugate of claim 1, wherein said polymer chain is absent fatty acids and glycolipids.

27. The conjugate of Claim 1, wherein said polymer chain is monomethoxypolyethylene glycol.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None